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Epidemiology
Tobacco and Geographic Pathology

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I. Introduction

Any treatise covering the pathogenesis of lung cancer would be incomplete without a summary of the relevant epidemiologic findings. This is so since epidemiologic observations have led to the identification of causes of this disease in human beings. Many of these observations have also determined the nature and extent of much of the laboratory work that has been done concerning this disease.

Because of the extent of the epidemiologic information about this disease, it should be a pleasure to review the subject. However, the success which has led to this storehouse of knowledge has also led to widespread dissemination of what is known. Therefore, it is difficult to summarize this information without becoming repetitive, and trite! Conversely, for the few areas in which substantive epidemiologic questions still remain, there are only few data. In these instances, critical review of the limited data available may not add much to our understanding. An attempt was made to keep these points in mind when this chapter was composed. The epidemiologic observations concerning the causes

of lung cancer can be related to (a) personal habits (tobacco usage), (b) occupational exposures, and (c) general demographic variables. The occupational exposures associated with increased lung cancer risk are covered in Chapter 2 in this book. This chapter will attempt to focus on the use of tobacco products, and perhaps the most interesting of the general demographic associations–geographic differences in risk.

II. Tobacco Use and Lung Cancer

The subject of tobacco use and the risk of lung cancer is so familiar that a detailed review seems unnecessary. This presentation attempts to point out the chronology of some of the earlier observations, summarize in a general form the basic associations which have been confirmed so many times, and then focus on a few of the currently unresolved issues on which research effort is, or should be, underway.

Historically, two very early reports suggested that the frequency of lung cancer was rising and related to environmental exposures [1, 2]. This was followed in the 1930s by observations indicating an excess of cigarette smokers among lung cancer patients [3, 4]. However, serious concern about the causative role of tobacco use in this disease did not arise until the late 1940s, when a marked increase in the frequency of lung cancer was linked to a marked increase in the use of tobacco products. In the early 1950s good case-control studies supported the role of cigarette smoking as the cause for the increase in the disease, and discounted other possible causes which had also been increasing simultaneously with the lung cancer rates [5, 6]. Since that time, numerous case-control and cohort (retrospective and prospective) studies have consistently identified the predominant role of cigarette smoking in this disease [7, 8]. Indeed, the consistency of results between studies conducted with markedly varying study designs and in markedly different situations has been truly remarkable. Equally remarkable has been the ease and consistency with which possible sources of bias have been shown not to influence the association between tobacco use and lung cancer. These have ranged from observations demonstrating that the increasing risk over time was real and not due to diagnostic artifact, to studies that have allowed control for numerous possible differences between lung cancer cases and comparison populations except for their cigarette smoking habits [9-11]. Indeed, perhaps the only remaining potential bias for which further assessment may be justified relates to the so-called constitutional hypothesis. This hypothesis contends that a certain type of person is determined by his genetic makeup to be predisposed to cigarette smoking and independently to developing lung cancer. This issue is covered in detail in a number of the reviews cited. Briefly, indirect evidence seems to indicate that this possible bias is not likely to be true. It certainly could not

explain the rapid increases over time in lung cancer, since gene pools do not change this rapidly. Also, thus far, control of all kinds of combinations of "constitutional" parameters has failed to diminish the risks associated with cigarette smoking. However, relevant studies continue to be conducted in this area, such as observations on twins who are discordant for smoking habits, and should clarify the issue over the next decade.

Some of the best summaries relating tobacco usage and lung cancer risk come from the reports of three large prospective studies. I will use these data to illustrate the major known associations. Owing to differences in the way the data are reported, it was not always possible to present information in precisely comparable groups for each study. The groupings presented (e.g., number of cigarettes smoked) should therefore be considered approximations, allowing roughly comparable observations between studies.

In 1951, Professors Doll and Hill initiated a study of 59,000 British physicians [12]. Comprehensive information concerning prior and current tobacco usage as well as information on a number of other variables was collected for each member of this group. The entire group has been followed from this time with periodic assessment of cigarette smoking practices, and continuous monitoring of mortality experience. In 1953 Harold Dorn initiated a study in the United States of 293,658 persons who were veterans of military service and policy holders of the U.S. Government Life Insurance, available to veterans who served between 1917 and 1940 [13]. Cigarette smoking habits and other information were obtained by mail questionnaire, with a response rate of 85%, and the mortality experience of this group has been periodically determined. In 1959 and 1960, Dr. E. Cuyler Hammond initiated a study of 1,078,894 men and women in order to assess the influence of smoking habits on the risk of disease [14, 15]. The study participants, enrolled by the volunteer workers of the American Cancer Society, Inc., resided in 1121 counties throughout the United States. Information on smoking habits and a number of other variables was obtained, and periodic monitoring of vital status, morbidity, and changes in smoking habits was carried out.

The risk of death from lung cancer by type of tobacco usage for each of these three studies is given in Table 1. The consistency between these three studies is remarkable. Those who smoked only cigars and/or pipes had a twofold increased risk of mortality from lung cancer. Those who smoked only cigarettes had a 10-fold increased risk. Those who smoked both cigarettes and cigars or pipes had a slightly lower risk than those who smoked only cigarettes. Table 2 gives the ratios of the mortality rates among cigarette smokers of various numbers of cigarettes to the rates experienced by nonsmokers. There is an impressive dose-response relationship between the risk of death from lung cancer and the number of cigarettes smoked per day, escalating to approximately a

TABLE 1 Relative Risk[a] of Death from Lung Cancer and Numbers of Deaths on Which They are Based[b] by Type of Smoking in Three Prospective Studies

Study	Type of smoking				
	Nonsmokers	Cigarettes only	Cigars only	Pipes only	Cigarette and other
Veterans [13] (Males only)	1.0 (78)	12.1 (749)	1.6 (25)	1.8 (17)	
American Cancer Society [15]					
Male	1.0 (83)	10.1 (1285)	2.2 (42)	2.2 (34)	8.2 (598)
Female	1.0 (166)	2.6 (161)	–	–	–
British physicians [12]					
Male	1.0 (3)	17.9 (133)	6.7 (21)		8.4 (36)
Female[c]	1.0	5.0	–	–	–

[a]Risk relative to a risk of 1.0 for nonsmokers. Calculated by dividing the age-adjusted death rate for lung cancer among smokers in various categories by that among nonsmokers.
[b]In parentheses.
[c]Only seven lung cancer deaths among all female British physicians in this study up to the time of the quoted report.

TABLE 2 Relative Risk[a] of Death from Lung Cancer and Number of Deaths on Which They are Based[b] among Continuing Cigarette (Only) Smokers by Number of Cigarettes Smoked per Day in Three Prospective Studies

Study	Number of cigarettes smoked per day			
	1-9	10-20	21-39	40+
Veterans [13] (Males only)	5.5 (45)	9.9 (303)	17.4 (315)	23.9 (82)
American Cancer Society [15]				
Males	4.6 (43)	8.6 (151)	14.7 (701)	18.8 (170)
Females	1.3 (15)	2.4 (34)	4.9 (85)	7.5 (12)
British Physicians[c] [12]				
Males	8.1 (22)		19.9 (54)	32.4 (57)
Females	–		13.7	7.3

[a]Same as Table 1, risk relative to that among nonsmokers.
[b]In parentheses.
[c]Groupings of cigarettes per day for the British study are 1-14, 15-24, and 25+.

TABLE 3 Relative Risk[a] of Death from Lung Cancer and Numbers of Deaths on Which They are Based[b] among Continuing Cigarette Smokers in the American Cancer Society's Prospective Study [15] According to the Age at Which They Began Smoking and Their Degree of Inhalation

	Male	Female
Age at starting to smoke		
<15	16.8 (185)	2.5 (6)
15–19	14.7 (588)	5.0 (52)
20–24	10.1 (196)	3.4 (34)
25+	4.1 (42)	2.3 (51)
Depth of inhalation		
None	8.0 (64)	2.0 (18)
Slight	8.9 (130)	2.3 (30)
Moderate	13.1 (595)	3.5 (66)
Heavy	17.0 (274)	7.1 (30)

[a] Same as Table 1, risk relative to that among nonsmokers.
[b] In parentheses.

20-fold risk among persons smoking two packs or more per day. The risk of lung cancer is also inversely proportional to the age at which smoking was begun and higher the greater the degree of inhalation (Table 3).

Although the trends described are in the same direction for both sexes, the magnitude of the ratios are not as high for women as they are for men. This is at least in part due to differences in amount of exposure. Cigarette smoking first became popular among men born after 1870, while it was not taken up by women until those born after 1900. In addition, as a group, women smoked fewer cigarettes per day, inhaled less deeply, and started the habit at an older age. While these patterns account for a substantial proportion of the discrepancies in the magnitude of the ratios, differences remain between the sexes in the magnitude of the effects of the same exposures.

The effect of ceasing to smoke is an important yet complex consideration in evaluating the risk of lung cancer. Two studies of this effect are shown in Table 4. Since almost every aspect of cigarette smoking (age started, amount smoked, number of years smoked, degree of inhalation) is so powerfully related to the risk of lung cancer, it is necessary to control for each of these variables in assessing the risk of lung cancer among ex-smokers. Although a thorough evaluation of this issue has not been made, it is clear that the risk of lung cancer declines as the interval of abstinence increases. Taken in the aggregate, the evidence also indicates that with appropriate control for all of the covariables (particularly duration of cigarette smoking), the risk probably never declines all the way to that experienced by nonsmokers.

TABLE 4 Relative Risk[a] of Death from Lung Cancer and Numbers of Deaths on Which They are Based[b] among Ex-Cigarette Smokers by Number of Years since Stopping in Two Prospective Studies

Study		Years since last smoked			
A. British Physicians		<0-4	5-9	10-19	20+
		9.6 (5)	7.0 (7)	2.6 (3)	2.7 (2)
B. American Cancer Society	Number[c]	<1	1-4	5-9	> 9
	1-19	7.1 (5)	3.3 (6)	1.3 (2)	0.4 (2)
	20+	17.1 (32)	10.1 (43)	6.5 (30)	1.8 (13)

[a]Same as Table 1, risk relative to that among nonsmokers.
[b]In parentheses.
[c]Number of cigarettes smoked per day (Group B).

There is much interest in the effect of smoking cigarettes with lower nicotine and tar content. Recent evidence indicates that individuals who smoke filter cigarettes experience a diminished relative risk of lung cancer compared to those who smoke nonfiltered cigarettes (Table 5).

It should be noted that it has been some time since the three large prospective studies have been updated. This is now being done with the goal of reporting on all three in some uniform fashion. These results should provide clarifying information on a number of points (e.g., ceasing to smoke, and the smoking of filter cigarettes).

The associations presented in the foregoing are those which have been reproduced with remarkable consistency in numerous studies. Although there is thus a large body of information concerning this exposure and disease complex, there are several areas needing good epidemiologic research that may ultimately provide important insights into carcinogenic mechanisms. These areas include the interaction between host and cigarette smoke, the effect on risk of ceasing to smoke, the potential for developing less hazardous cigarettes, and the interactions between cigarette smoking and other environmental exposures.

Since the vast majority of smokers, even heavy smokers, do not develop lung cancer, it is clear that a number of other variables are involved in the carcinogenic process. Perhaps the most important covariable is that of host susceptibility. Much recent interest has been stimulated by a preliminary report of differences between lung cancer cases and controls in the inducibility of aryl hydrocarbon hydroxylase activity in peripheral lymphocytes [17]. That the

TABLE 5 Relative Risks[a] of Lung Cancer (Kreyberg I)[b] among Nonfilter Cigarette Smokers and Those Smoking Filter Cigarettes for >10 Years in One Case-Control Study [16] by Number of Cigarettes Smoked per Day

	Number of cigarettes smoked per day			
Type of cigarette	1-10	11-20	21-40	41+
Filter	6	18	31	118
Nonfilter	30	31	50	200

[a]Risk of occurrence of lung cancer relative to the risk of nonsmokers.
[b]Kreyberg I: Pathologic class of carcinomas of the lung including the epidermoid and oat cell types (those histologic types showing the strongest association with cigarette smoking).

carcinogenic potential of hydrocarbons might be related to an individual's ability to metabolize them is certainly reasonable; if this association holds up under closer scrutiny, the prospects for intensified studies of host-exposure interactions would certainly be heightened. This area is covered in more detail in Chapters 3 and 11 of this monograph.

The evaluation of the risk of disease in ex-smokers is one of prime importance to epidemiologists. Because of the small numbers of such individuals in previous studies, our understanding of these risks is only starting to emerge. For a proper evaluation, account has to be taken of the age when cigarette smoking began, and the duration and intensity of smoking. Only when these factors are adequately controlled can an appropriate evaluation of risk among ex-smokers be made, according to the interval after cessation of smoking. That the risk of lung cancer drops with the number of years an ex-smoker has remained abstinent is clear. However, as the prospective studies begin to yield more data on this point, it appears that cigarette smokers can greatly reduce their chance of developing lung cancer by stopping, but they also will have already incurred some increased baseline risk that is not reversible [18].

Because of the failure of antismoking campaigns to lower the prevalence of the habit in this country, much interest has turned toward the development of less hazardous cigarettes. The feeling has been that if the carcinogenic agent in cigarette smoke is contained in the total particulate matter (tar), then the production of cigarettes which deliver less of this material in inhaled combustion products should lead to relatively lower risks of lung cancer. Since the late 1950s there has been an obvious acceptance of this idea by the consumer, as the tar and nicotine contents of the best selling United States cigarettes have dropped dramatically during this time [16]. While adequate data are only now emerging, it appears that individuals smoking filter cigarettes are at lower risk of lung cancer than those smoking the nonfilter varieties, although clearly still

far in excess of the risk among nonsmokers [19]. Further studies of this issue are badly needed. In addition, there is a need for parallel assessment of other diseases associated with cigarette smoking, to determine if the reduction in carcinogenic potential is accompanied by lower (or perhaps higher) risks of other disorders associated with this habit [20].

Finally, more research is required to evaluate the interaction of cigarette smoking with other environmental exposures. It is curious that our current knowledge about biological interactions between carcinogens has come mainly from observations on cigarette smokers exposed to other environmental agents. The risk of lung cancer associated with cigarette smoking and inhalation of radioactive dust among uranium miners is clearly not additive but much closer to being multiplicative [21]. The situation with occupational exposure to asbestos is even more dramatic. Whereas the risk of lung cancer in cigarette smokers is approximately 10-fold, the risk among smoking asbestos workers is around 90-fold [22]. Although there is not yet a large amount of data on nonsmoking asbestos workers, the risk in relative terms is probably not large. In addition, while it does not relate to lung cancer, cigarette smoking and alcohol ingestion seem also to be biologically synergistic in producing cancers of the oral cavity, esophagus, and larynx [23]. Although the number of interactions observed between cigarette smoking and other environmental exposures may simply reflect the large amount of information collected concerning cigarette smoking, the possibility that the carcinogens in cigarette smoke may lend themselves biologically to such interactions should be kept in mind. In the future this may prove particularly important in assessing the effects of various levels of pollutants in the air we breathe and the water we drink, since the risks associated with these chronic, low-level exposures may be different among smokers than among nonsmokers.

III. Geographic Pathology of Lung Cancer

There is considerable variation in the rates of lung cancer between various countries in the world. Figure 1 illustrates the pattern of this variation, ranked on magnitude of the rate among males. As illustrated, the incidence rates are highest in the United Kingdom and lowest in Asia and Africa. Rates for most areas in North America and Europe are scattered between these two extreme values. It should also be noted that, for the most part, the relative ranking of the rates among females does not closely parallel that among males.

The prominent position of many westernized countries comes from the markedly increased rates attributable to cigarette smoking. Indeed, the inclusion of the Maori of New Zealand with the high-risk westernized countries is

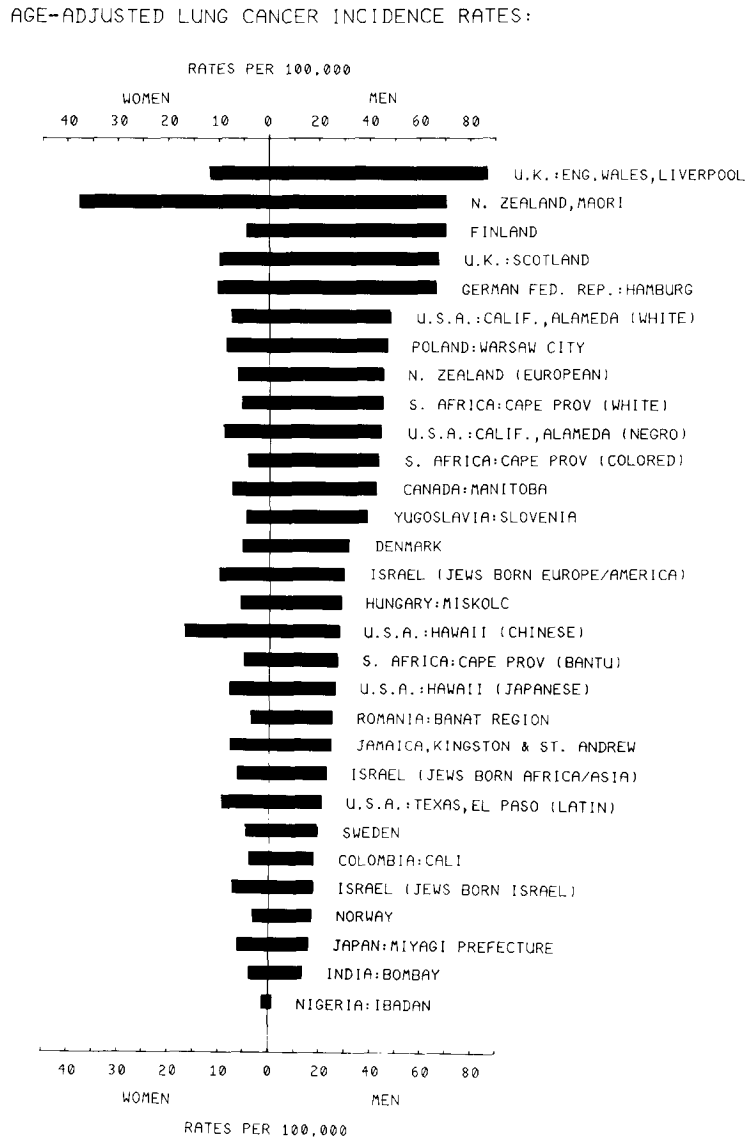

FIGURE 1 Age-adjusted lung cancer incidence rates for men and women in various countries. (From Ref. 24.) (*Note*: The scales used for presentation are different for the two sexes.)

undoubtedly due to the long-standing and heavy use of tobacco products by both sexes [25]. In addition, cigarette smoking is probably responsible for much of the disparity between the relative ranking of the rats for females and those for males. The increase in lung cancer rates among women came considerably after the increase for men and occurred to a much lesser extent. This seemed to correspond well with the later onset of the prominent use of tobacco products among women and the generally lower relative risks associated with tobacco use among women.

There are a number of other possible explanations for some of the variation seen in Figure 1. Among these are urban/rural differences. A consistent finding in almost every descriptive study done in numerous countries is that the rates in urban areas exceed those in rural areas. This may reflect differences in cigarette smoking practices, occupational exposures, and/or general environmental exposures. There also appear to be racial or ethnic differences which migrant studies suggest may be due to environmental factors. The risk of lung cancer among a migrant group tends to move away from the rate in the country of origin and toward that of the host country.

Although international variation and time trends in lung cancer provided leads to the identification of cigarette smoking as a cause of lung cancer, there is some question as to the value of these comparisons now, in helping to detect other causes of this disease. This stems from the overpowering nature of the association with cigarette smoking itself. Only slight differences in amount of smoking, or age at beginning to smoke, could lead to major differences in lung cancer rates for the general population. Since controlling for these subtle differences in exposure may be impossible in a descriptive study, the identification of other causes for observed variations in risk is made extremely difficult.

There may be several exceptions to this general rule, however. Perhaps two of the more intriguing differences in Figure 1 are the high rates among Chinese females in Hawaii and the wide variation in rates between the various Scandinavian countries. Excessive rates of lung cancer among Chinese women have been noted in Singapore [26, 27], California [28], and in the total United States [29], as well as in Hawaii. An added unusual feature of these excesses is that they may be due to adenocarcinoma of the lung [27, 30], a relatively infrequent histologic form of lung cancer elsewhere in the world. Little has been done to follow up these intriguing epidemiologic observations, and more intensive pathologic and epidemiologic studies of lung cancer among the Chinese certainly seem warranted. The disparity in the level of lung cancer between the various Scandinavian countries (Finland quite high, Denmark intermediate, and Sweden and Norway quite low) is another intriguing observation that might warrant further investigation.

Although international patterns of lung cancer have been thoroughly examined, comparatively little has been done with respect to variation within countries. This type of study of geographic variation has certain distinct advantages in limiting the number of plausible explanations for observed differences. While differences in smoking habits could account for regional differences in lung cancer risk within a country, marked differences in rates between areas that are quite close to each other geographically and demographically would seem unlikely to be attributable solely to differences in smoking patterns.

A study of the geographic patterns of lung cancer mortality by individual counties of the United States has recently been completed [31-33]. Figures 2 and 3 illustrate the variation in risk among white men and women residing in the 3056 counties of the continental United States. Figures 4 and 5 illustrate the geographic pattern for lung cancer mortality among nonwhite men and women according to the 506 state economic areas (collections of counties with similar economic, demographic, and social compositions).

Considerable geographic variation is noted, with high rates in Northern urban areas and among males along large stretches of the Gulf and South Atlantic coasts. Indeed, much of this variation is explicable on the basis of urbanization (Table 6). Rates increase with urbanization for both sexes in each geographic region. Furthermore, within rural areas, farming areas have lower rates than rural nonfarm areas. In addition, however, high rates among males were associated with the presence of certain industries. Specifically, excessive rates were noted in counties where paper, chemical, petroleum, and transportation (shipbuilding) industries were located. These associations were not due to urbanization, socioeconomic, or other industrial or demographic factors (Figs. 6-8), and may account for at least part of the excess lung cancer risk in Southern coastal areas.

This consistent variation with degree of urbanization and presence of certain specific industries indicates that the amount of lung cancer attributable to occupational exposures may be more than currently suspected. A similar conclusion comes from data from one of the large prospective studies of cigarette smoking and lung cancer [15]. After controlling for age and cigarette smoking, appreciable excesses in risk were noted for men who claimed to be occupationally exposed to "dust, fumes, vapors, gases, or x-rays." Since the exposures included under this gross categorization undoubtedly include short-term exposures to noncarcinogenic substances, the excess risk associated with significant exposure to certain occupational hazards may be quite large. Perhaps one meaningful direction to take from geographic and correlational studies is to attempt to discover previously unrecognized occupational causes of lung cancer that may apply to larger numbers of workers than those specific agents already identified as industrial lung carcinogens.

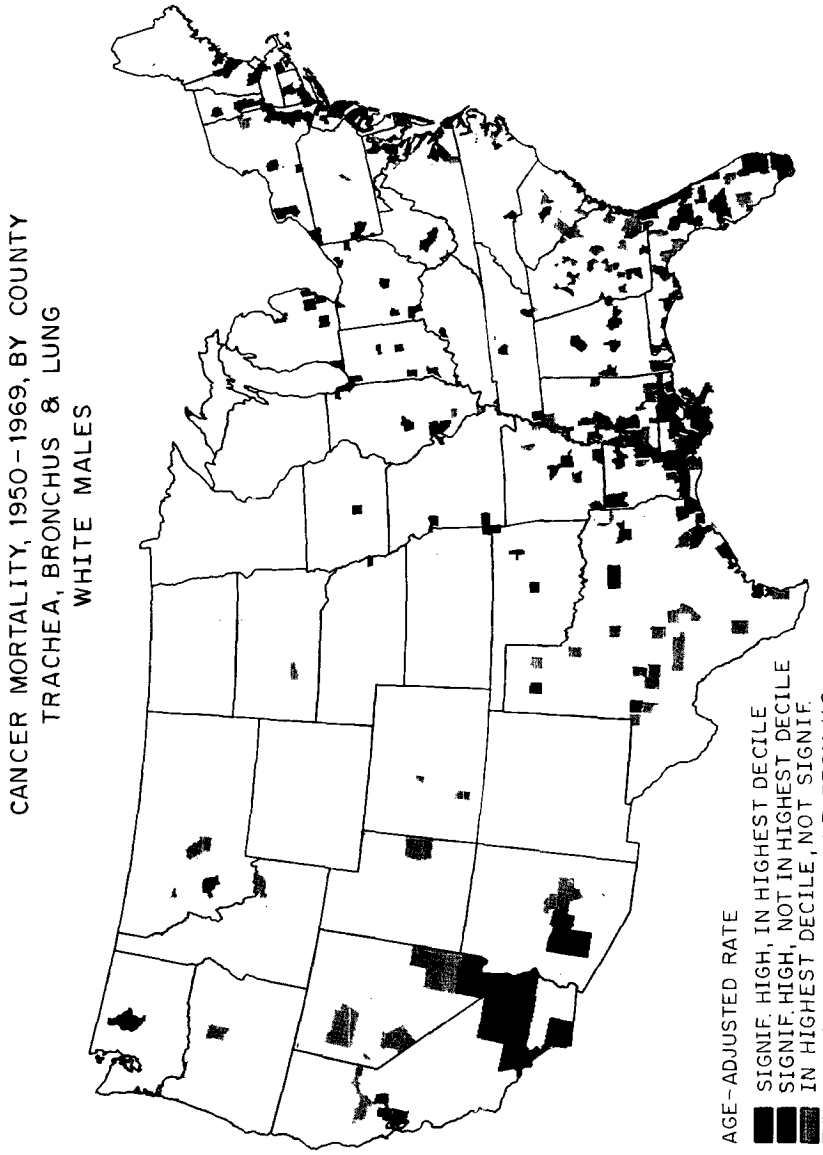

FIGURE 2 Age-adjusted lung cancer mortality rates among white males (1950-1969) for the 3056 counties of the continental United States. (From Ref. 30.)

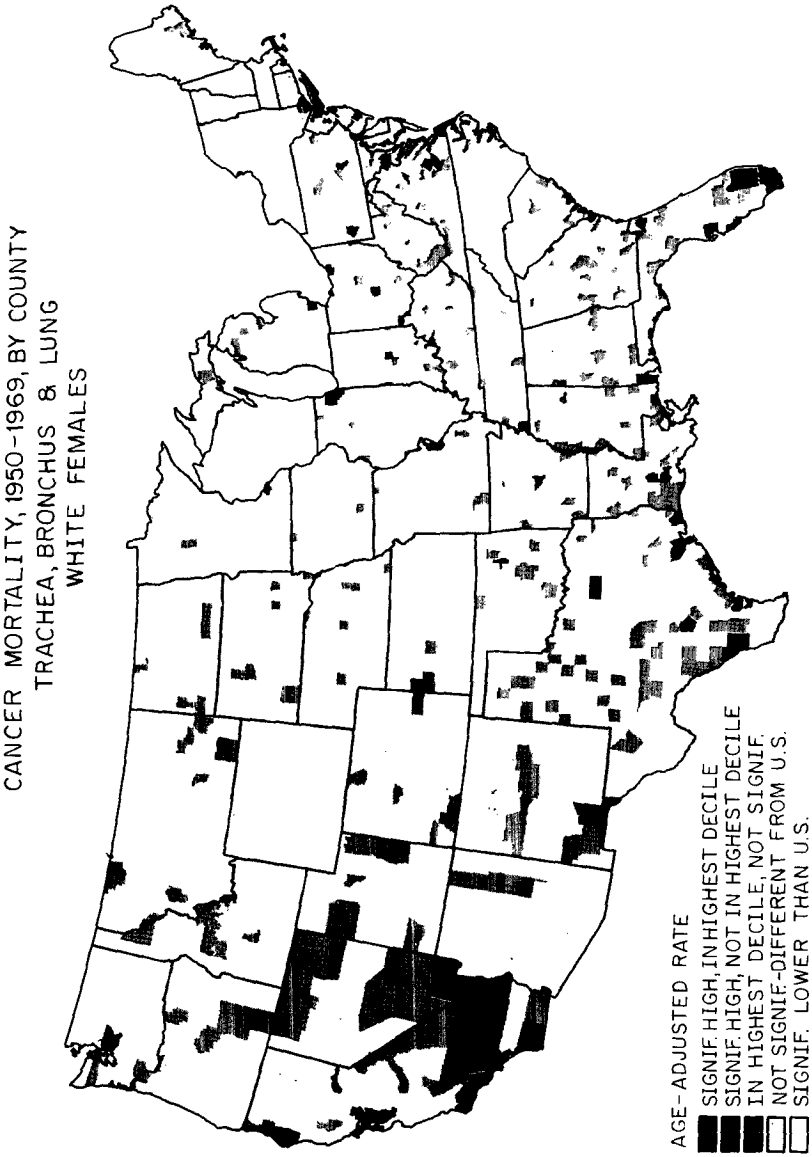

FIGURE 3 Age-adjusted lung cancer mortality rates among white females (1950–1969) for the 3056 counties of the continental United States. (From Ref. 30.)

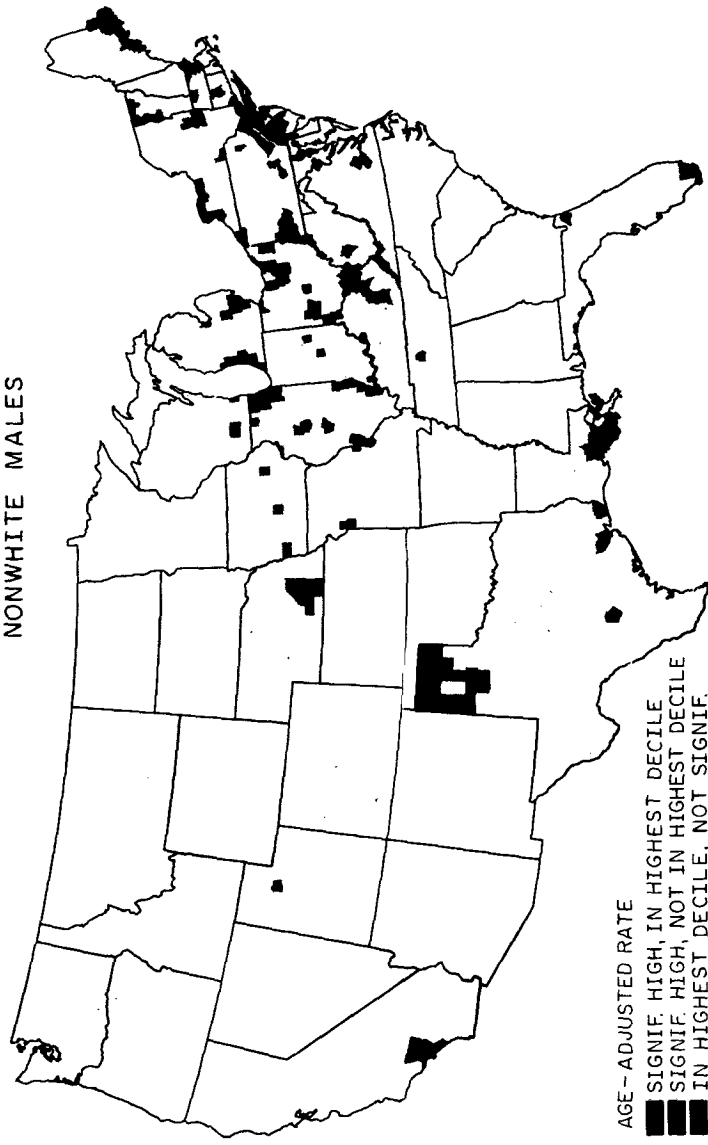

FIGURE 4 Age-adjusted lung cancer mortality rates among nonwhite males (1950–1969) for the 506 state economic areas (aggregations of counties) of the continental United States. (From Ref. 31.)

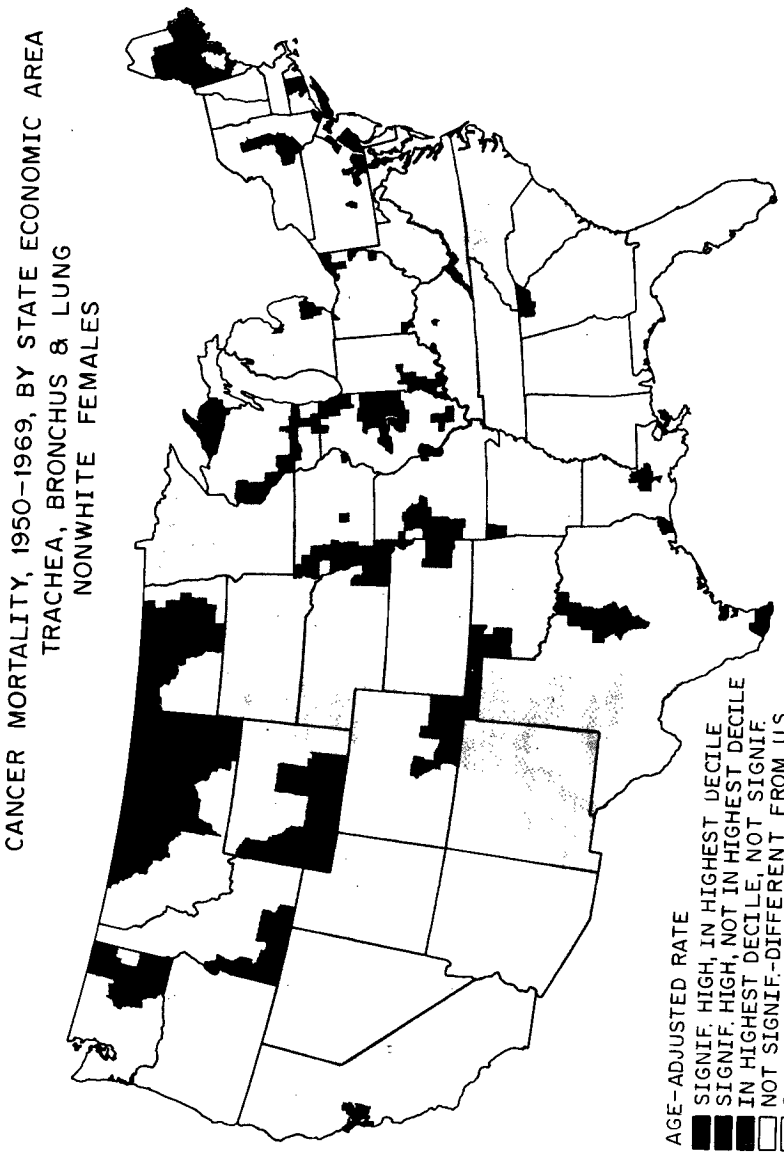

FIGURE 5 Age-adjusted lung cancer mortality rates among nonwhite females (1950–1969) for the 506 state economic areas (aggregations of counties) of the continental United States. (From Ref. 31.)

TABLE 6 Average Annual Age-Adjusted Mortality Rates per 100,000 for Lung Cancer in Whites (1950-1969) among U.S. Counties Grouped by the Percentage of Their Population Residing in an Urban Area

Percent urban	Males	Females
0-24.9	26.9	4.9
25-49.9	30.5	5.1
50-74.9	33.2	5.5
75+	39.9	6.5

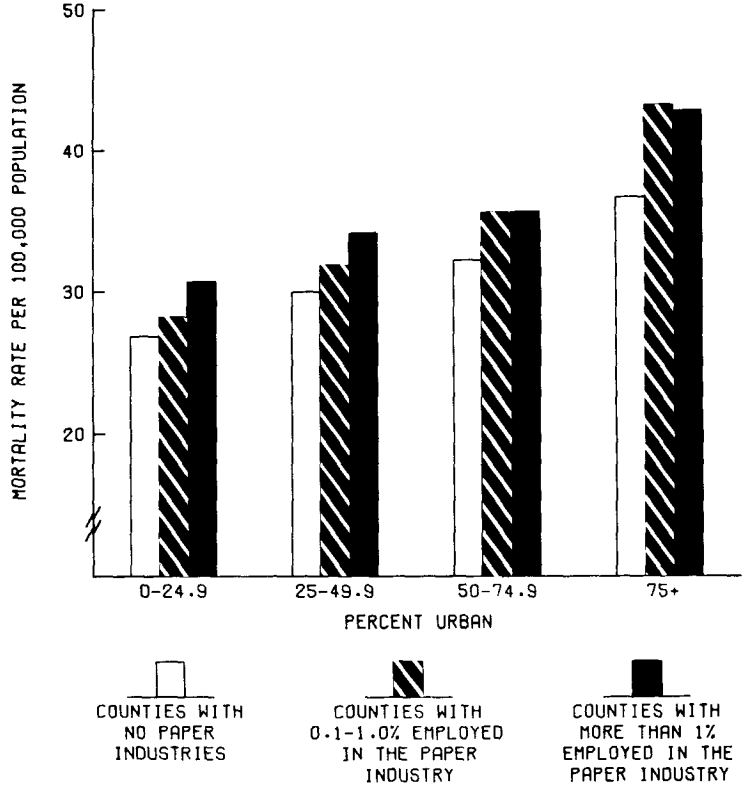

FIGURE 6 Average annual age-adjusted mortality rates for lung cancer among white males (1950-1969) in paper industry counties. (From Ref. 32; reprinted with permission.)

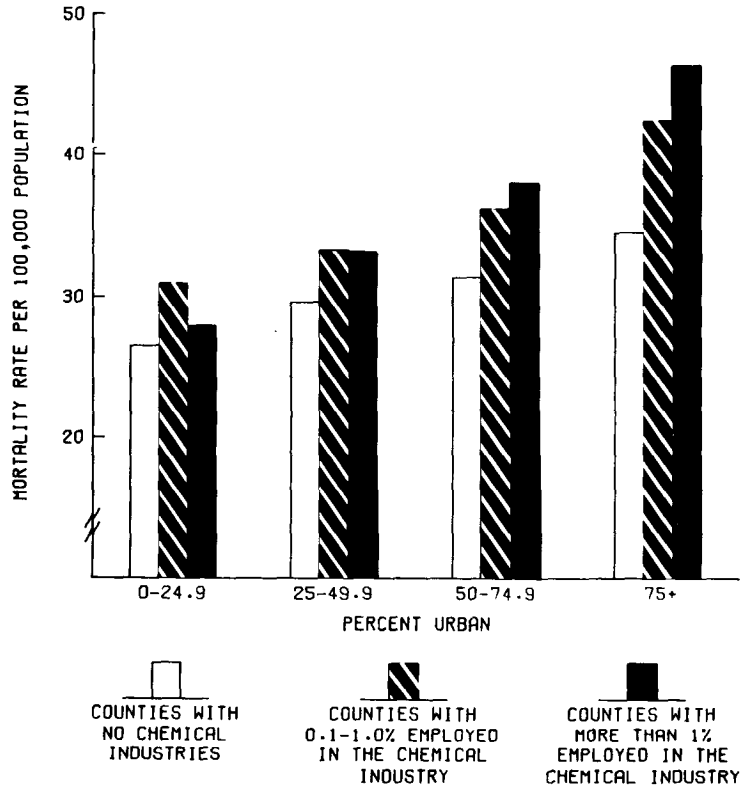

FIGURE 7 Average annual age-adjusted mortality rates for lung cancer among white males (1950–1969) in chemical industry counties. (From Ref. 32; reprinted with permission.)

As yet there has not been an adequate evaluation of the effects of chronic, long-term exposure to low levels of air pollution in the general environment. The difficulties with doing an adequate epidemiologic evaluation of these exposures are myriad and have been well documented by others. Specifically, "air pollution" is a general term covering a variety of exposures which vary dramatically from one "polluted" area to another. In addition, the actual exposure of inhabitants in an area can vary quite dramatically depending on differences in life-style, which are dictated by such things as socioeconomic class and occupation. Finally, because of the overpowering nature of the cigarette smoking association, there is a great need to achieve fine control for cigarette smoking in attempting to assess small relative increases in risk due to other exposures.

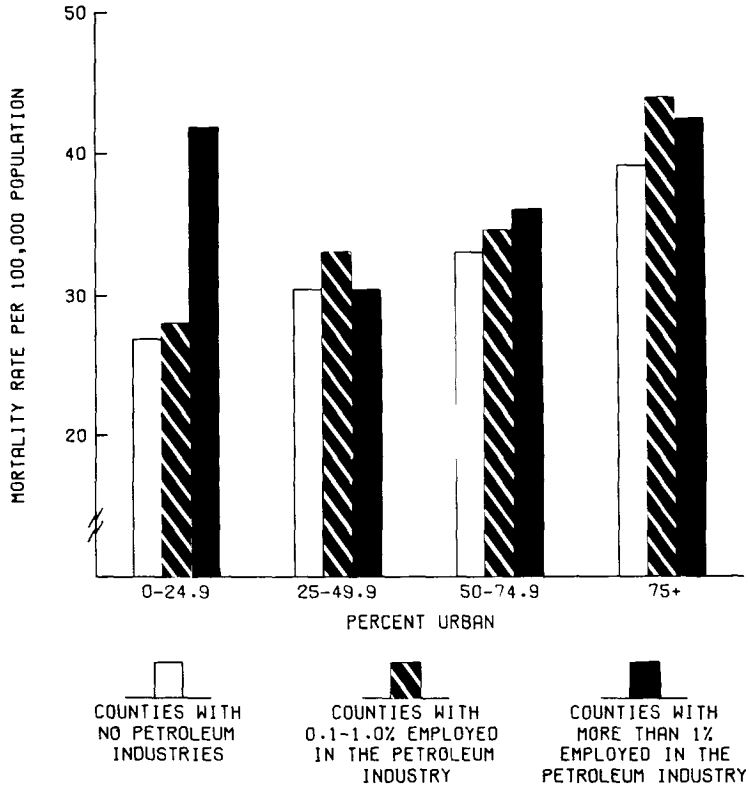

FIGURE 8 Average annual age-adjusted mortality rates for lung cancer among white males (1950–1969) in petroleum industry counties. (From Ref. 32; reprinted with permission.)

Given all of this, the ability of geographic studies to give us clues to general environmental determinants of lung cancer remains to be determined.

Before giving up in this general area, however, two points concerning this subject should be kept in mind. The prospective study which has given us valuable information on the risk of cigarette smoking and the likely presence of significant occupational hazards, has also attempted to evaluate the role of urban environments independent of cigarette smoking and occupation [15]. This evaluation has been generally regarded as nonsupportive of a significant role for general environmental pollution in the development of lung cancer. However, several consistent, significantly decreasing gradients in risk were presented progressing from city to town or rural area and thence to farm.

The differences were not large in relative terms, and certain biases could not be ruled out. However, with the heterogeneous categorization of exposure, and the relatively small increases in risk that one might be looking for, this study could just as easily be interpreted as a positive study. Furthermore, the authors of this study point out that categorizing people differently might lead to different results. Specifically, grouping people who lived close to a heavily polluting source of known or suspect carcinogens would be a much more appropriate way of evaluating risk. With this in mind, a study of lung cancer in counties with large, nonferrous metal smelters has recently been completed [34]. These industries have emitted large quantities of inorganic arsenic into the general environment. Significantly elevated lung cancer rates were found in men and women which could not be explained on the basis of urbanization or other demographic or industrial factors (Figs. 9 and 10).

Perhaps then, in certain instances, studies of intracounty variation in lung cancer risk could identify areas of unusual risk which might be explicable on the basis of a community exposure. Specific analytic studies designed to test the hypotheses raised could then be carried out in these areas. Alternatively, as

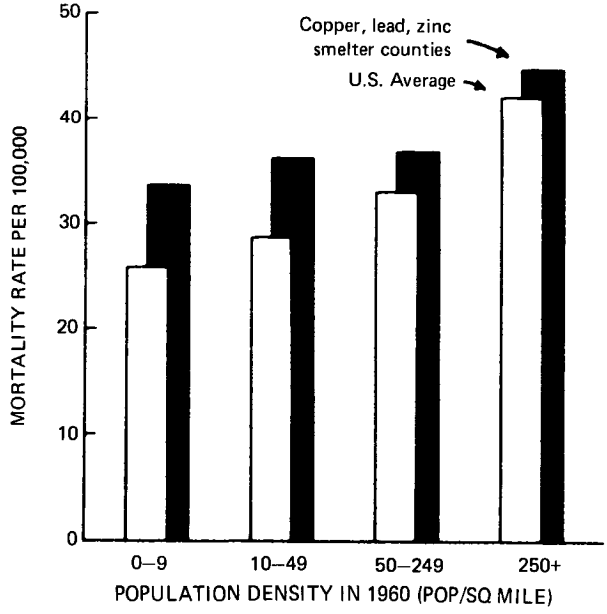

FIGURE 9 Average annual age-adjusted lung cancer mortality rates among white males (1950-1969) in U.S. counties according to the presence of nonferrous metal smelters and population density. (From Ref. 33.)

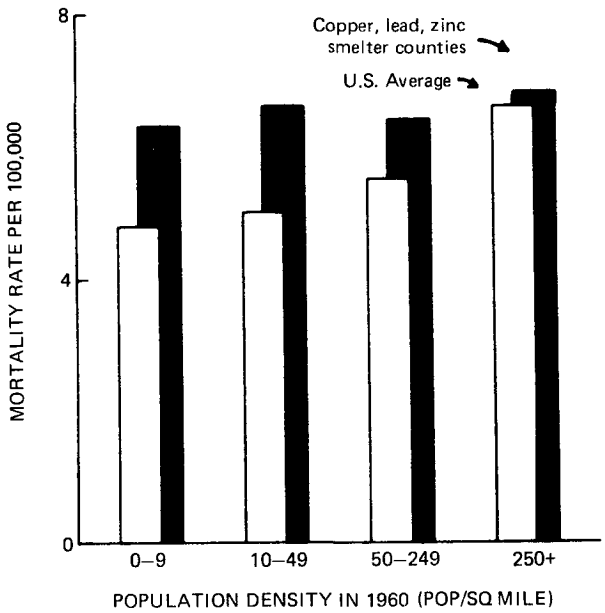

FIGURE 10 Average annual age-adjusted lung cancer mortality rates among white females (1950–1969) in U.S. counties according to the presence of nonferfous metal smelters and population density. (From Ref. 33.)

measurements of environmental pollution improve, perhaps areas of unusually high exposure could be defined and appropriately grouped so that some initial, descriptive evaluation could be done in order to help set priorities for future work.

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